Association of energy and fat intake with prostate carcinoma risk: results from The Netherlands Cohort Study.

Association of Energy and Fat Intake with Prostate Carcinoma Risk

Results from the Netherlands Cohort Study

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BACKGROUND. The roles of energy and fat intake as risk factors for prostate carcinoma are still questionable. Therefore, these factors were evaluated in the Netherlands Cohort Study described in this article.

METHODS. The cohort study consisted of 58,279 men ages 55–69 years at baseline in 1986. After 6.3 years of follow-up, 642 incident prostate carcinoma cases were available for analysis. Intake of energy, fat, and separate fatty acids were measured by means of a self-administered questionnaire; fat intake was adjusted for energy by regression analysis. The case–cohort method was used to calculate rate ratios (RRs). Analyses were conducted for all prostate carcinoma cases together as well as for case subgroups (latent vs. nonlatent and localized vs. advanced).

RESULTS. No associations were found in multivariate analyses between prostate carcinoma and intake of energy, total fat, total saturated fatty acids, or total *trans* unsaturated fatty acids (RR highest vs. lowest quintile: 0.99, 1.10, 1.19, and 0.99, respectively). Oleic acid intake showed a nonsignificant positive association (RR = 1.38, 95% CI: 0.88–2.19). Positive associations were also observed for intake of oleic acid in subgroup analyses. Linoleic (RR = 0.78, 95% CI: 0.56–1.09) and linolenic (RR = 0.76, 95% CI: 0.66–1.04) acid intake were associated with nonsignificantly decreased risks; only for linolenic acid did these associations persist in subgroup analyses. No associations were found for intake of arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.

CONCLUSIONS. These data suggest that certain fatty acids might be involved in prostate carcinoma occurrence, although the possibility that these were chance findings cannot be ruled out. ***Cancer* 1999;86:1019–27.**
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KEYWORDS: prostate neoplasms, energy, fat, fatty acids, intake, cohort study.

Prostate carcinoma incidence and mortality are increasing.[1] In many Western countries, prostate carcinoma is one of the most frequently occurring types of cancer among men. Because clinical prostate carcinoma shows a noteworthy geographic variation in incidence compared with latent prostate carcinoma, environmental risk factors, among which are energy and fat intake, are thought to play an important role in the etiology of clinical prostate carcinoma.[2–5]

The relation between fat intake and prostate carcinoma risk was summarized in several reviews on (dietary) risk factors for the disease.[2–6] In these reviews it is most often concluded that fat intake is positively related to prostate carcinoma risk. However, these conclusions are based on not only fat intake per se, but also results regarding consumption of meat, milk, and other dairy products. In one of the reviews it is concluded that there is no conclusive evidence of a role

for fat in prostate carcinoma etiology.[2] Furthermore, specific fatty acids have been investigated in few studies.[7–14] Nevertheless, in some studies a positive association of α-linolenic acid[9,10,12] and oleic acid[10,12] with risk of prostate carcinoma has been shown. It has been proposed that clinically apparent or advanced prostate tumors might have a different etiology than latent tumors. Only a minority of all studies of fat and prostate carcinoma risk examined fat intake for latent and nonlatent or localized and advanced tumors separately,[9,10,13,15–17] with diverse results.

Underlying biologic mechanisms explaining a possible effect of fat intake on prostate carcinoma risk are not clear, but some mechanisms have been proposed. Increased fat intake might lead to increased testosterone levels, and this might eventually lead to increased cell division, activation of proto-oncogenes, and deactivation of tumor suppressor genes.[18] A role of specific fatty acids in prostate tumor occurrence is biologically plausible, because essential fatty acids are a source of metabolic energy and are required for membrane structure and for the synthesis of intermediate compounds that are important for cellular metabolism.[19] Linoleic and linolenic acid are both precursors of eicosanoid production, and eicosanoids have been shown to be related to tumor development (including cell proliferation, immune response, invasion, and metastasis).[10,20] In vitro, linoleic acid has been shown to stimulate the growth of some but not all prostate cell lines,[19,20] and the same is true of linolenic acid.[19] For docosahexaenoic acid and eicosapentaenoic acid, growth inhibitory effects have been reported,[20] but at low concentrations eicosapentaenoic acid has also been reported to stimulate tumor promotion.[19] Finally, another potential mechanism to explain an effect of fatty acids may be free radical formation resulting from the oxidation of fatty acids.[9,10]

In this article, we present our findings regarding fat intake and prostate carcinoma risk from the Netherlands Cohort Study (NLCS), which was specifically designed to examine diet in relation to cancer. Findings are also presented with respect to latent and nonlatent, as well as localized and advanced, prostate tumors.

METHODS

The Cohort

The study design has been described elsewhere.[21] In brief, the NLCS was initiated in September 1986. The male cohort consisted of 58,279 men ages 55–69 years who completed a self-administered questionnaire on their usual diet and other risk factors for cancer. Subjects originated from 204 municipal population registries throughout the country. For reasons of efficiency in data processing and analysis, the case–cohort approach[22] was used. In a case–cohort approach, cases are derived from the entire cohort (providing numerator information for calculation of cancer incidence rates), whereas accumulated person-years at risk in the total cohort are estimated using a random male subcohort sample (providing denominator information for the rates). In contrast to nested case–control sampling, this subcohort can be used for multiple disease endpoints. The male subcohort was sampled directly after identification of the total cohort and included 1688 men. The method of cancer follow-up has also been described previously.[23] In short, incident primary prostate carcinoma cases were detected by computerized record linkage with all nine cancer registries in The Netherlands and with the Dutch national data base of pathology reports (PALGA). The subcohort was followed up biennially for vital status information. No subcohort members were lost to follow-up, and completeness of follow-up of cancer was at least 96%.[24] After a follow-up period of 6.3 years (September 1986 to December 1992), 704 incident, microscopically confirmed, primary prostate carcinoma cases were detected.

The Questionnaire

The self-administered questionnaire has been described elsewhere.[25] Usual consumption of food and beverages during the year preceding the start of the study was assessed with a 150-item semiquantitative food frequency questionnaire. Among the principal nutrients of interest were energy and fat intake. Questionnaire data were key-entered twice and processed for all incident cases in the cohort and for all subcohort members in a manner blinded with respect to case/subcohort status. This was done to minimize observer bias in coding and interpretation of the data. Mean daily nutrient intakes were calculated using the computerized Dutch food composition table.[26] Intake of specific fatty acids was based on a food composition data base with specific fatty acids, including *trans* fatty acids, derived from the TRANSFAIR study.[27] For this data base, the 100 foods that contributed most to fat intake in the Dutch dietary pattern were sampled and analyzed as methyl esters of the fatty acids present in the foods. In the data base, total fat included triglycerides and other lipids, such as phospholipids and sterols. The percentage of triglycerides in total fat is assumed to be 93% on average, but it varies across food sources. In the data base for the NLCS, the concentrations of fatty acids were based on the concentrations before 1995, when changes in the *trans* con-

tent of manufactured products, such as margarines, led to a decrease in the intake of *trans* fatty acids.

Data Analysis

In the subcohort, prevalent cancer cases at baseline other than skin cancer were excluded, leaving 1630 subcohort members for analysis. Furthermore, according to criteria published previously,[25] subjects with incomplete or inconsistent dietary data were excluded; 642 men with prostate carcinoma and 1525 male subcohort members remained for analysis.

Exposure variables included in the current analysis were intake of total energy, total fat, total fatty acids, saturated fatty acids, monounsaturated and polyunsaturated fatty acids, *trans* unsaturated fatty acids, *cis* unsaturated fatty acids, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid. Fat intake was adjusted for energy by regression analysis.[28] Mean intake levels of exposure variables and other characteristics were compared between prostate carcinoma cases and male subcohort members. Furthermore, mean intakes of total energy and total fat intake were compared in categories of potential confounders. Rate ratios (RR) and 95% confidence intervals (95% CI) were computed for quintiles of energy and fat intake, as well as for continuous variables of intake, using the GLIM statistical package.[29] Exponentially distributed survival times were assumed in the follow-up period. Because standard software was not available, specific macros were developed to account for the additional variance introduced by using the subcohort instead of the entire cohort.[30] Throughout this report, two-sided P values are given; trend tests for quintile ranks were based on likelihood ratio tests. Age-adjusted and multivariate analyses were conducted. Variables that were considered as potential confounders were age, family history of prostate carcinoma, and socioeconomic status. For all energy-adjusted variables, energy intake was also included in the multivariate model, in conformity with the method described by Willett.[28] In addition, to assess the independent contribution of saturated fatty acids, monounsaturated and polyunsaturated fatty acids, and each specific fatty acid, total energy-adjusted fat intake was also included in the multivariate model. Vegetable and fruit consumption and intake of vitamin E were not considered as potential confounding factors because no association with prostate carcinoma risk was observed.[31] In additional analyses, cases detected during the first 2 years of follow-up were excluded to evaluate whether preclinical disease may have influenced results.

Subgroup Analyses

Separate analyses were conducted for latent and nonlatent tumors, for continuous variables of exposure. The subgroups were constructed based on information about surgical procedures mentioned in the pathology reports obtained from PALGA. Tumors that were detected as a consequence of transurethral prostate resections, usually performed for problems associated with benign prostatic hyperplasia (BPH), were coded latent. Nonlatent tumors were those tumors that were detected as a consequence of procedures used in case of suspected cancer (biopsy, radical prostatectomy). Cases were excluded from these subgroup analyses when this additional information was unknown or unclear (38.2%). Because population screening for prostate carcinoma was not instituted before 1992 in The Netherlands, we assumed there were no tumors detected by screening in the 6.3 years of follow-up. Analyses were also conducted for localized prostate tumors (T0–2, M0: no evidence of primary tumor [T0], clinically unapparent tumor [T1], or tumor confined within the prostate [T2], and no distant metastasis [M0]) and advanced prostate tumors (T3–4, M0 or T0–4, M1: tumor extending through prostatic capsule [T3], fixed tumor or tumor invading adjacent structures other than seminal vesicles [T4], and no distant metastasis [M0]; or any tumor [T0–4] with distant metastasis [M1]), based on the TNM classification system.[32] Of all cases, 31.6% could not be categorized in localized or advanced tumors.

RESULTS

In Table 1, the mean intake of energy and energy-adjusted fat intake among cases and subcohort members is shown. The mean energy intake was somewhat lower among cases than among subcohort members. Overall, mean fat intake did not differ to a large extent between cases and subcohort members. Also shown in this table is the distribution of potential confounding factors. Cases were older than subcohort members, more often had a positive family history of prostate carcinoma, and were more highly educated than subcohort members. Comparing total energy and fat intake across categories of potential confounding factors showed that total energy intake was highest at younger ages and in the lowest category of socioeconomic status. Total fat intake did not differ across categories of potential confounding factors (data not shown).

Age-adjusted and multivariate adjusted RRs for prostate carcinoma according to total energy and total fat intake, as well as grouped fatty acids, are summarized in Table 2. Multivariate adjusted RRs were sim-

TABLE 1
Description of Mean Energy and Energy-Adjusted Fat Intake and Distribution of Potential Confounding Variables in Prostate Carcinoma Cases and Male Subcohort Members, Netherlands Cohort Study, at 6.3 Years of Follow-Up (1986–1992)

Characteristics	Cases (n = 642) Mean (SD)	Subcohort (n = 1525) Mean (SD)
Exposure variables (g/day)		
Energy intake (kcal/day)	2115 (487)	2157 (513)
Total fat[a]	94.1 (13.3)	93.6 (14.4)
Total fatty acids[b]	87.5 (12.8)	87.0 (13.8)
Total saturated fatty acids	36.9 (8.5)	36.3 (8.4)
Total monounsaturated fatty acids	28.5 (5.1)	28.3 (5.2)
Total polyunsaturated fatty acids	20.2 (7.7)	20.5 (8.2)
Total *trans* unsaturated fatty acids	3.3 (1.4)	3.3 (1.3)
Total *cis* unsaturated fatty acids	45.4 (9.6)	45.6 (10.1)
Palmitic acid	18.6 (3.7)	18.4 (3.8)
Stearic acid	8.3 (1.4)	8.2 (1.6)
Oleic acid	21.7 (4.4)	21.6 (4.3)
Linoleic acid	18.0 (7.7)	18.2 (8.1)
Linolenic acid	1.3 (0.6)	1.4 (0.6)
Arachidonic acid	0.11 (0.04)	0.11 (0.05)
Eicosapentaenoic acid	0.05 (0.06)	0.04 (0.05)
Docosahexaenoic acid	0.09 (0.09)	0.08 (0.08)
Potential confounding variables		
Age (yrs)	63.9 (3.8)	61.4 (4.2)
Family history of prostate carcinoma (% yes)	4.4	2.7
Highest educational level (%)[c]		
Low	44.7	47.1
Medium	34.9	35.0
High	20.4	17.9

[a] Includes other lipids such as phospholipids.
[b] Includes about 2% unidentified fatty acids.
[c] Low is defined as primary school with or without lower level vocational education, medium as secondary school or medium level vocational education, and high as university or higher level vocational education.

ilar to age-adjusted risk estimates. No associations were observed for intake of total energy, total fat, total fatty acids, saturated fatty acids, and *trans* unsaturated fatty acids. A nonsignificant slightly increased risk was noted for intake of monounsaturated fatty acids (RR highest vs. lowest quintile = 1.32, 95% CI: 0.82–2.12). Nonsignificant inverse associations were indicated for intake of polyunsaturated fatty acids (RR = 0.78, 95% CI: 0.56–1.10) and intake of *cis* unsaturated fatty acids (RR = 0.80, 95% CI: 0.54–1.20). When *cis* unsaturated fatty acids were separated in monounsaturated and polyunsaturated *cis* fatty acids, the RR comparing highest versus lowest quintile for *cis* monounsaturated fatty acids was somewhat increased (RR = 1.34, 95% CI: 0.84–2.14), whereas the RR for *cis* polyunsaturated fatty acids was slightly decreased (RR = 0.77, 95% CI: 0.55–1.08). However, both estimates were nonsignificant and there was no trend in risk (data not shown).

In Table 3, the RRs for the intake of specific fatty acids in relation to prostate carcinoma risk are shown. Again, age-adjusted and multivariate adjusted RRs were very similar. For most individual fatty acids, no clear associations with prostate carcinoma were observed. Only for intake of oleic acid was a nonsignificant slightly increased risk observed (RR = 1.38), but there was no trend in risk. In the highest intake quintiles, both for intake of linoleic acid and linolenic acid nonsignificant decreased risks were observed (RR = 0.78 and 0.76, respectively), but the trend test was not significant in either case. Exclusion of cases detected during the first 2 years of follow-up did not change the results presented in Tables 2 and 3 (data not shown).

In Table 4, results from multivariate analyses for continuous variables of energy and fat intake are presented for all prostate carcinoma cases and separately for latent, nonlatent, localized, and advanced tumors. For most exposure variables, no clear associations were observed in the different subgroups and, overall, associations were mostly similar in latent and nonlatent, and localized and advanced, tumor subgroups. Nonsignificant increased risk estimates were found for intake of monounsaturated fatty acids in association with latent and nonlatent tumors and for oleic acid in association with all four tumor subgroups. Inverse associations were observed in subgroups of latent, nonlatent, and localized tumors for linolenic acid intake.

DISCUSSION

In the NLCS, we found no association between intake of energy, total fat, total fatty acids, saturated fatty acids, and *trans* unsaturated fatty acids and overall prostate carcinoma risk. For specific fatty acids, a positive association with prostate carcinoma risk was indicated for oleic acid intake, also in subgroup analyses. An inverse association was indicated for intake of linoleic acid and linolenic acid. The trend test for linolenic acid intake was significant in the age-adjusted analysis. Results in subgroups were less clear.

Before discussing the results in relation to those of other studies, some remarks about the NLCS are relevant. Loss to follow-up is the primary source of potential selection bias in prospective cohort studies. Given the high completeness of follow-up of the cases and subcohort person-years in the NLCS,[24,33] selection bias is unlikely. In the case of prostate carcinoma, symptoms of the disease (e.g., urethral obstruction) are unlikely to cause a change in dietary fat intake. Nevertheless, we conducted analyses after exclusion of cases diagnosed in the first 2 years of follow-up, and the results were similar to our overall results.

The questionnaire has been validated against a

TABLE 2
Rate Ratios (RR) and 95% Confidence Intervals (95% CI) for Prostate Carcinoma According to Quintiles of Intake of Energy and Energy-Adjusted Fat, Netherlands Cohort Study, at 6.3 Years of Follow-Up (1986–1992)

Exposure	Q1[a]	Q2	Q3	Q4	Q5	*P* value for trend
Energy intake						
Median intake[b]	1541	1870	2117	2377	2803	
Cases/person-years	133/1804	141/1803	129/1831	135/1836	104/1848	
RR[c] (95% CI)	1.00	1.08 (0.80–1.46)	0.97 (0.72–1.32)	1.08 (0.80–1.46)	0.98 (0.71–1.36)	0.94
RR[d] (95% CI)	1.00	1.05 (0.78–1.43)	0.95 (0.70–1.30)	1.04 (0.77–1.41)	0.99 (0.72–1.37)	0.93
Total fat						
Median intake[e]	76.0	87.2	94.0	100.3	110.4	
Cases/person-years	114/1804	139/1828	132/1853	132/1806	125/1831	
RR[c] (95% CI)	1.00	1.24 (0.91–1.69)	1.12 (0.82–1.54)	1.10 (0.81–1.51)	1.11 (0.81–1.52)	0.81
RR[f] (95% CI)	1.00	1.22 (0.89–1.67)	1.10 (0.80–1.51)	1.10 (0.80–1.51)	1.10 (0.80–1.52)	0.78
Total fatty acids						
Median intake[e]	70.1	80.9	87.3	93.5	103.5	
Cases/person-years	110/1804	146/1820	127/1864	133/1812	126/1822	
RR[c] (95% CI)	1.00	1.36 (1.00–1.86)	1.07 (0.78–1.47)	1.14 (0.84–1.57)	1.15 (0.84–1.58)	0.77
RR[f] (95% CI)	1.00	1.32 (0.97–1.82)	1.04 (0.76–1.44)	1.13 (0.82–1.56)	1.14 (0.83–1.57)	0.77
Saturated fatty acids						
Median intake[e]	26.4	31.7	35.5	40.0	47.5	
Cases/person-years	129/1814	115/1822	128/1812	103/1864	167/1809	
RR[c] (95% CI)	1.00	0.91 (0.67–1.25)	0.96 (0.71–1.31)	0.75 (0.54–1.03)	1.23 (0.91–1.65)	0.27
RR[g] (95% CI)	1.00	0.88 (0.63–1.24)	0.93 (0.65–1.32)	0.75 (0.51–1.08)	1.19 (0.80–1.76)	0.43
Monounsaturated fatty acids						
Median intake[e]	22.3	25.8	28.2	30.6	34.3	
Cases/person-years	120/1780	133/1846	144/1849	117/1827	128/1821	
RR[c] (95% CI)	1.00	1.16 (0.85–1.59)	1.26 (0.93–1.71)	1.00 (0.73–1.37)	1.22 (0.89–1.67)	0.39
RR[g] (95% CI)	1.00	1.22 (0.87–1.71)	1.30 (0.90–1.88)	1.07 (0.72–1.60)	1.32 (0.82–2.12)	0.48
Polyunsaturated fatty acids						
Median intake[e]	11.0	15.9	19.8	24.1	31.1	
Cases/person-years	135/1807	101/1833	150/1819	142/1843	114/1821	
RR[c] (95% CI)	1.00	0.71 (0.52–0.98)	1.14 (0.85–1.54)	1.01 (0.75–1.37)	0.80 (0.58–1.09)	0.71
RR[g] (95% CI)	1.00	0.73 (0.53–1.01)	1.15 (0.84–1.56)	1.00 (0.73–1.37)	0.78 (0.56–1.10)	0.52
Trans unsaturated fatty acids						
Median intake[e]	1.9	2.6	3.2	3.7	4.7	
Cases/person-years	119/1795	136/1824	135/1830	136/1829	116/1844	
RR[c] (95% CI)	1.00	1.22 (0.89–1.66)	1.18 (0.86–1.60)	1.13 (0.83–1.54)	1.01 (0.73–1.39)	0.87
RR[g] (95% CI)	1.00	1.25 (0.90–1.72)	1.20 (0.86–1.65)	1.12 (0.80–1.55)	0.99 (0.70–1.40)	0.72
Cis unsaturated fatty acids						
Median intake[e]	34.2	40.2	45.0	51.1	58.1	
Cases/person-years	135/1821	122/1814	127/1812	142/1847	116/1829	
RR[c] (95% CI)	1.00	0.93 (0.69–1.27)	1.00 (0.74–1.37)	1.03 (0.76–1.39)	0.89 (0.65–1.22)	0.67
RR[g] (95% CI)	1.00	0.90 (0.65–1.24)	0.94 (0.67–1.32)	0.96 (0.68–1.35)	0.80 (0.54–1.20)	0.34

[a] Reference category.
[b] Median intake (kcal/day) in subcohort.
[c] Adjusted for age.
[d] Adjusted for age, family history of prostate carcinoma, and socioeconomic status.
[e] Median intake (g/day) in subcohort.
[f] Adjusted for age, family history of prostate carcinoma, socioeconomic status, and total energy intake.
[g] Adjusted for age, family history of prostate carcinoma, socioeconomic status, total energy intake, and total energy-adjusted fat intake.

9-day diet record. Crude (and energy-gender-adjusted) Pearson correlation coefficients between the dietary record and the questionnaire were as follows: energy, 0.74; total fat, 0.72 (0.52); saturated fat, 0.73 (0.58); polyunsaturated fat, 0.73 (0.75).[25] From this validation study, we conclude that fat intake was reasonably well measured in our self-administered semiquantitative questionnaire. The correlation coefficient of 0.52 for total fat intake was most likely a consequence of the relatively homogeneous dietary fat in-

TABLE 3
Rate Ratios (RR) and 95% Confidence Intervals (95% CI) for Prostate Carcinoma According to Quintiles of Intake of Specific Energy-Adjusted Fatty Acids, Netherlands Cohort Study, at 6.3 Years of Follow-Up (1986–1992)

Exposure	Q1[a]	Q2	Q3	Q4	Q5	*P* value for trend
Palmitic acid						
Median intake[b]	13.9	16.5	18.3	20.2	23.2	
Cases/person-years	110/1802	136/1816	128/1834	137/1860	131/1811	
RR[c] (95% CI)	1.00	1.38 (1.01–1.90)	1.14 (0.83–1.56)	1.19 (0.87–1.63)	1.16 (0.85–1.60)	0.62
RR[d] (95% CI)	1.00	1.37 (0.98–1.91)	1.14 (0.80–1.62)	1.20 (0.83–1.74)	1.14 (0.75–1.74)	0.79
Stearic acid						
Median intake[b]	6.4	7.4	8.2	8.9	10.1	
Cases/person-years	105/1804	133/1831	140/1810	133/1854	131/1823	
RR[c] (95% CI)	1.00	1.15 (0.84–1.59)	1.28 (0.94–1.76)	1.06 (0.77–1.45)	1.17 (0.85–1.61)	0.49
RR[d] (95% CI)	1.00	1.18 (0.84–1.67)	1.35 (0.93–1.94)	1.12 (0.75–1.66)	1.23 (0.78–1.94)	0.57
Oleic acid						
Median intake[b]	16.8	19.6	21.5	23.4	26.3	
Cases/person-years	113/1795	152/1829	131/1864	118/1807	128/1827	
RR[c] (95% CI)	1.00	1.45 (1.06–1.97)	1.18 (0.86–1.62)	1.10 (0.80–1.52)	1.30 (0.94–1.78)	0.45
RR[d] (95% CI)	1.00	1.47 (1.05–2.06)	1.23 (0.85–1.79)	1.17 (0.78–1.76)	1.38 (0.88–2.19)	0.48
Linoleic acid						
Median intake[b]	9.0	13.6	17.1	21.4	28.8	
Cases/person-years	135/1813	101/1824	144/1824	144/1836	118/1825	
RR[c] (95% CI)	1.00	0.69 (0.50–0.95)	1.05 (0.78–1.42)	1.06 (0.78–1.43)	0.80 (0.58–1.09)	0.89
RR[d] (95% CI)	1.00	0.71 (0.51–0.98)	1.04 (0.77–1.42)	1.05 (0.77–1.44)	0.78 (0.56–1.09)	0.68
Linolenic acid						
Median intake[b]	0.7	1.1	1.3	1.7	2.1	
Cases/person-years	154/1802	126/1820	125/1808	123/1838	114/1855	
RR[c] (95% CI)	1.00	0.80 (0.59–1.08)	0.82 (0.61–1.11)	0.80 (0.59–1.08)	0.76 (0.56–1.03)	0.04
RR[d] (95% CI)	1.00	0.76 (0.55–1.05)	0.82 (0.60–1.13)	0.80 (0.59–1.10)	0.76 (0.66–1.04)	0.09
Arachidonic acid						
Median intake[b]	0.06	0.09	0.11	0.13	0.17	
Cases/person-years	113/1781	133/1849	151/1879	113/1783	132/1830	
RR[c] (95% CI)	1.00	1.23 (0.90–1.69)	1.38 (1.01–1.88)	1.10 (0.80–1.53)	1.20 (0.87–1.64)	0.40
RR[d] (95% CI)	1.00	1.21 (0.88–1.66)	1.37 (1.00–1.87)	1.11 (0.80–1.54)	1.20 (0.87–1.66)	0.30
Eicosapentaenoic acid						
Median intake[b]	0.00	0.01	0.03	0.05	0.10	
Cases/person-years	135/1918	102/1853	125/1790	138/1771	142/1790	
RR[c] (95% CI)	1.00	0.69 (0.50–0.95)	0.94 (0.69–1.28)	1.06 (0.79–1.44)	1.01 (0.75–1.37)	0.11
RR[d] (95% CI)	1.00	0.66 (0.47–0.91)	0.92 (0.67–1.27)	1.05 (0.77–1.44)	1.00 (0.73–1.35)	0.10
Docosahexaenoic acid						
Median intake[b]	0.01	0.03	0.06	0.09	0.18	
Cases/person-years	124/1846	111/1834	128/1811	139/1836	140/1796	
RR[c] (95% CI)	1.00	0.82 (0.60–1.13)	1.01 (0.74–1.38)	1.07 (0.79–1.46)	1.05 (0.77–1.42)	0.19
RR[d] (95% CI)	1.00	0.81 (0.58–1.11)	1.00 (0.73–1.38)	1.09 (0.80–1.49)	1.03 (0.75–1.40)	0.19

[a] Reference category.
[b] Median intake (g/day) in subcohort.
[c] Adjusted for age.
[d] Adjusted for age, family history of prostate carcinoma, socioeconomic status, total energy intake, and total energy-adjusted fat intake.

take in our study population. For polyunsaturated fat intake, however, the range in intake was much higher and the correlation coefficient from our validation study was 0.75. To prevent substantial misclassification, we excluded subjects with incomplete or inconsistent data. A possible misclassification of fat intake is likely to be nondifferential, thus leading to a bias towards the null value. Besides a validation study, five annually repeated measurements of the food frequency questionnaire were conducted. From the results, it was concluded that the single measurement of intake of diet in the NLCS can characterize dietary habits for a period of at least 5 years.[34] Furthermore, our study population consisted of older subjects (ages 55–69 years) who were chosen because, in general, they show more stable dietary habits than younger

TABLE 4
Rate Ratios (RR) and 95% Confidence Intervals (95% CI) per 10 g Increment for Prostate Carcinoma, According to Intake of Energy and Energy-Adjusted Fat, for All Cases and in Subgroups Based on Tumor Characterization; Netherlands Cohort Study, at 6.3 Years of Follow-Up (1986–1992)

		Tumor subgroups		Tumor subgroups	
Exposure	All tumors (n = 642)	Latent tumors (n = 115)	Nonlatent tumors (n = 282)	Localized (n = 226)	Advanced (n = 213)
Energy intake					
RR[a,b] (95% CI)	1.00 (0.98–1.02)	1.01 (0.97–1.05)	1.00 (0.97–1.02)	1.03 (1.00–1.06)	0.99 (0.96–1.02)
Total fat					
RR[c] (95% CI)	1.02 (0.95–1.09)	1.07 (0.93–1.22)	1.00 (0.91–1.10)	1.03 (0.93–1.14)	1.00 (0.90–1.11)
Total fatty acids					
RR[c] (95% CI)	1.02 (0.95–1.10)	1.08 (0.93–1.24)	1.00 (0.91–1.10)	1.03 (0.93–1.15)	1.01 (0.90–1.12)
Saturated fatty acids					
RR[d] (95% CI)	1.09 (0.92–1.28)	1.02 (0.72–1.43)	1.06 (0.84–1.33)	1.08 (0.86–1.36)	1.02 (0.80–1.31)
Monounsaturated fatty acids					
RR[d] (95% CI)	1.25 (0.89–1.75)	1.45 (0.76–2.75)	1.30 (0.84–2.02)	1.12 (0.70–1.80)	1.23 (0.74–2.03)
Polyunsaturated fatty acids					
RR[d] (95% CI)	0.91 (0.80–1.04)	0.91 (0.70–1.18)	0.94 (0.79–1.12)	0.93 (0.77–1.12)	0.98 (0.80–1.19)
Trans unsaturated fatty acids					
RR[d] (95% CI)	1.06 (0.48–2.33)	0.99 (0.22–4.55)	1.11 (0.39–3.14)	0.93 (0.30–2.86)	0.76 (0.21–2.71)
Cis unsaturated fatty acids					
RR[d] (95% CI)	0.94 (0.82–1.08)	0.96 (0.74–1.26)	0.97 (0.81–1.16)	0.94 (0.78–1.14)	1.02 (0.83–1.25)
Palmitic acid					
RR[d] (95% CI)	1.17 (0.79–1.75)	1.34 (0.61–2.92)	0.99 (0.59–1.68)	1.07 (0.61–1.89)	1.09 (0.60–2.00)
Stearic acid					
RR[d] (95% CI)	1.06 (0.37–3.01)	1.52 (0.20–11.62)	0.66 (0.17–2.60)	0.74 (0.17–3.18)	0.92 (0.19–4.45)
Oleic acid					
RR[d] (95% CI)	1.32 (0.90–1.91)	1.50 (0.75–3.02)	1.43 (0.88–2.34)	1.22 (0.72–2.08)	1.43 (0.82–2.50)
Linoleic acid					
RR[d] (95% CI)	0.92 (0.81–1.05)	0.92 (0.71–1.19)	0.94 (0.79–1.12)	0.94 (0.78–1.13)	0.98 (0.80–1.19)
Linolenic acid					
RR[d] (95% CI)	0.22 (0.04–1.36)	0.26 (0.00–9.20)	0.20 (0.02–2.31)	0.14 (0.00–1.93)	1.12 (0.08–16.18)
Arachidonic acid					
RR[d,e] (95% CI)	1.06 (0.85–1.32)	0.79 (0.50–1.24)	1.04 (0.77–1.39)	0.90 (0.65–1.25)	1.11 (0.80–1.54)
Eicosapentaenoic acid					
RR[d,e] (95% CI)	1.15 (0.96–1.38)	1.14 (0.80–1.62)	1.02 (0.80–1.32)	0.97 (0.73–1.29)	1.11 (0.84–1.45)
Docosahexaenoic acid					
RR[d,e] (95% CI)	1.08 (0.96–1.21)	1.08 (0.86–1.36)	1.00 (0.85–1.17)	0.95 (0.79–1.15)	1.09 (0.92–1.29)

[a] Adjusted for age, family history of prostate carcinoma, and socioeconomic status.
[b] RR per increment of 100 kcal.
[c] Adjusted for age, family history of prostate carcinoma, socioeconomic status, and total energy intake.
[d] Adjusted for age, family history of prostate carcinoma, socioeconomic status, total energy intake, and total energy-adjusted fat intake.
[e] RR per increment of 0.1 g.

individuals.[21] Nevertheless, if diet in early adulthood might be important in prostate carcinoma etiology, our results might not reflect these effects.

Finally, residual confounding cannot be ruled out, and it is also important to note that multiple comparisons were made in our study. Therefore, although the power of the NLCS (based on 642 cases and 1525 subcohort members) was large, chance played a role in our findings and one needs to be stringent in interpreting the data.

Some remarks about other studies of energy and fat intake and prostate carcinoma risk are also appropriate. First, most evidence of fat intake in relation to prostate carcinoma risk comes from case–control studies,[7,8,13–17,35–45] and there are only six cohort studies on the topic.[9–12,46,47] In general, case–control studies are more prone to bias than cohort studies. Second, there were only a few cohort studies[9,10,12] and case–control studies[13,15,16,37,43,44] that extensively evaluated the role of energy and fat intake. Other

studies had limited exposure information. In addition, only a minority of studies took energy intake into account in evaluating fat intake.[9,13,15,16,43–45] Third, in several studies only limited adjustment for other possible confounders was made, and residual confounding may have influenced results. Finally, evidence from earlier studies of fat in relation to prostate carcinoma risk is mostly based on a number of cases that was less than the 642 cases used in our study. To date, the largest cohort study of fat intake in relation to prostate carcinoma risk comprised 300 cases.[9]

For intake of energy, total fatty acids, saturated fatty acids, and monounsaturated and polyunsaturated fatty acids, no strong associations with overall risk of prostate carcinoma were observed in our study. In several other studies, associations were also not reported for energy,[44–46] total fat,[9,12,13,15,17,37–39,42,45,46] saturated fat,[9,13,45,46] unsaturated fat,[37,46] monounsaturated fat,[12,13,16,45] and polyunsaturated fat.[12,13,16,43,45] Nevertheless, positive associations have been reported for energy,[13,15,43] total fat,[16,35,36,40,41] saturated fat,[12,15,16,37] and monounsaturated[9,15] and polyunsaturated fat,[15,44] whereas inverse associations for energy,[39] total fat,[43,44] saturated fat,[43,44] and monounsaturated fat have been noted.[43,44]

The principal saturated fatty acids in the diet are palmitic and stearic acid, for which we found no clear associations. In previous studies, for serum levels of palmitic acid, both no association[10] and a positive association[12] were reported, and for serum levels of stearic acid, both a null association[12] and an inverse association[10] were observed. For oleic acid, the principal monounsaturated fatty acid in the diet, we observed a positive association. Positive associations have been reported previously for serum levels of oleic acid[10,12] but not for intake levels.[7,8] Our results indicated an inverse association between prostate carcinoma risk and intake of linoleic and linolenic acid. The suggested inverse association between prostate carcinoma risk and linoleic acid intake gains support from another cohort study using serum levels,[10] but in some other studies associations were less clear[9,12,13] or even positive.[14] In other studies of linolenic acid, mostly increased estimates have been reported,[10,12,14] sometimes only for advanced tumors;[9] and in one study no association was found.[13] Finally, we found no clear associations for intake of arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid. Other studies also did not report clear or strong associations for these fatty acids.[9,10,12,14]

For none of our exposure variables of interest, except for intake of oleic acid, did we find a stronger association with nonlatent or advanced prostate tumors. Our results, however, need to be interpreted carefully, because a considerable proportion of cases could not be classified into tumor subgroups. Two case–control studies also did not find evidence that fat intake was more strongly related to risk of advanced tumors than to overall prostate carcinoma risk.[12,13] Furthermore, in some other studies it was found that excluding focal microscopic cancers[10] or diffuse latent cancers[17] did not change results. However, in one cohort study, total fat intake and intake of α-linolenic acid were positively associated with advanced tumors, and not with all tumors.[9] In one case–control study, only saturated fat intake showed a stronger positive association with advanced tumors than with all prostate tumors,[16] and in another case–control study fat intake had a consistently stronger association with aggressive prostate tumors, but only for men age 68 years or older.[15] Thus far, conclusions indicating that fat intake is particularly associated with advanced or aggressive prostate tumors seem preliminary.

In conclusion, in our study we found no evidence of a strong association between energy or fat intake, or intake of a number of specific fatty acids, and prostate carcinoma risk. However, there was a suggestion of a positive association for intake of oleic acid and inverse associations for intake of linoleic acid and linolenic acid. Findings from other studies are very diverse, also with respect to nonlatent or advanced prostate tumors. More studies with extensive exposure information are needed to clarify the role of specific fatty acids in prostate carcinoma etiology.

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